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09/885,287	06/21/2001	Andreas Sewing	MERCK-2261	2670

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EXAMINER
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LANDAU, SHARMILA GOLLAMUDI

ART UNIT	PAPER NUMBER
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1611

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PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 09/885,287	<b>Applicant(s)</b> SEWING ET AL.	
	<b>Examiner</b> Sharmila Gollamudi Landau	<b>Art Unit</b> 1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 31 October 2007.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1,3-8,10,12-19,21 and 23-28 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,3-8,10,12-19,21 and 23-28 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                     | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date: _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date: _____   | 6) <input type="checkbox"/> Other: _____                          |

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### **DETAILED ACTION**

Receipt Request for Continued Examination and Amendments/Remarks filed 10/31/07 is acknowledged. Claims **1, 3-8, 10, 12-19, 21, and 23-28** are pending in this application. Claims 2, 9, 11, 20, and 22 stand cancelled.

#### ***Miscellaneous Remarks***

All NPL documents submitted for consideration must be cited in a PTO-1449. Therefore, Biomimetic Materials Chemistry has been placed in the file but has not been considered.

#### ***Duplicate Claim Objection***

Claim 23 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 10. Claim 7 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 17. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

#### ***Claim Objections***

Claim 16 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 16 is directed to the metallic implant of claim 1, wherein the mineralized collagen matrix is layered. However, claim 1 is directed to a mineralized collagen matrix that is constructed in the form of layers.

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Claim 16 objected is also objected to for the following misspelling: “mineralised”.

Appropriate correction is required.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

**Claims 1, 4, 8, 10, 12-16, 18-19, 21, 23-25, and 27-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 11-047259 in view of Constantz et al (5,279,831) optionally in further view of Lussi et al (5,167,961) as evidenced by US 5,543,441.**

JP teaches a prosthetic implant coated with hydroxyapatite (HA). The implants provide an implant that is close to osseous tissue and such implants fully “unite with existing osseous tissue and will promote growth of the new bone”. [002]. The coating contains highly crystalline hydroxyapatite and low content of amorphous calcium phosphate. See abstract. The examples teaches coating a titanium-alloy implant. The coating also has a low content of tricalcium phosphate and doped with carbonate. See examples and [0080].

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JP does not teach the particle size of HA or collagen.

Constantz teaches a hydroxyapatite prosthesis coating which allows for ingrowth of natural bone. See abstract. The method involves combining a soluble source of calcium with a soluble source of phosphate under conditions of controlled nucleation and modulated crystal growth to form a multilayered hydroxyapatite coating on a substrate. Constantz teaches the use of other ions and components to modify the HA composition such as using fluoride, carbonate, hydrogen, etc, which influence the dissolution behavior of the coating. see column 2, lines 50-60. Constantz teaches the coating composition may further comprises collagen and growth factors to enhance bony ingrowth. See column 6, lines 1-10. The composition is coated on a steel or titanium. See column 6, lines 14-20. The crystals have a diameter of 0.01microns (10nm) to 20 microns (20000nm) (see column 2, line 60) and a length of 0.01 microns (10nm) to about 10 microns (10000nm) (see column 3, line 40). Constantz teaches a first layer of the coating with a thickness of 0.01microns (10nm) to 20 microns (20000nm). See column 3, lines 39-41.

Lussi et al teach a process for preparing high purity bone mineral for implantation. See abstract. Lussi teaches natural bone mineral comprises hydroxyapatite-like crystallites with a particular degree of crystallinity, habit and size (irregular platelike morphology, 5-10nm in thickness 10-50 nm in length) and surface chemistry resulting from the calcium to phosphate ratio (37.5-38.0% calcium and 15.5-5-19.0% phosphorus). See column 1, lines 15-35. Lussi teaches prior art methods of making the bone mineral result in significant increase in crystal size which is much less readily remodelled on implantation since osteoclasts and osteoblasts cannot readily perform on such large crystals the dual function of mineral resorption and generation of new bone. Such implanted inserts may thus remain unchanged indefinitely eventually giving rise

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to undesirable effects. Lussi teaches, alternatively, many synthetic tricalcium phosphate products tend to be resorbed too rapidly for osteoblasts to regenerate new bone. See column 1, lines 49-60. The process provides HA particles having a size from 20nm to 250; 100nm to 300nm; and 100nm to 400nm and a diameter of 34nm or 130 nm depending on the temperature used. See Table 1. Lussi teaches the HA particles have a similar structure to original bone. See column 4, lines 1-10. Lussi teaches it is important to avoid modification of the crystal sizes to ensure when the bone is implanted, it is readily converted into natural bone. See column 5, lines 18-30. The bone mineral according to the invention may thus be used as a remodelling implant or prosthetic bone replacement, for example in orthopedic surgery, including hip revisions, replacement of bone loss e.g. in traumatology, remodelling in maxillo facial surgery or filling periodontal defects and tooth extraction sockets. The bone mineral may also have adsorbed or absorbed therein one or more physiologically active substances including drugs or polypeptides, and proteins. See column 4, lines 30-60 and column 5, lines 10-20.

Firstly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of JP and Constantz et al and further add collagen to the hydroxyapatite coating. One would have been motivated to do so since Constantz teaches a HA coating composition that may further comprise collagen and growth factors to enhance bone growth. A skilled artisan would have reasonably expected similar results since both references are in the same filed of endeavor, i.e. implants coated with hydroxyapatite compositions. With regard to claim 4, a skilled artisan would have been motivated to add other ions such as fluoride or carbonate to manipulate the resorption rate of the coating. Further, Constantz teaches various particles sizes of HA that are suitable for HA coating compositions.

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Secondly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teaching of JP and Lussi et al and specifically utilize the instant particle size. One would have been motivated to do so since Lussi teaches that HA particles with the instant particle size resorb better and cause generation of new bone faster. Further, Lussi teaches natural bone has the instant particle size. Thus, a skilled artisan would have been motivated to utilize the instant particle size since it closely resembles natural bone and allows for the body to convert the particles to natural bone faster. A skilled artisan would have reasonably expected similar results since JP teaches the purpose of the hydroxyapatite coating on implants since to provide a surface for bone ingrowth and to mimic natural bone.

Regarding the product-by-process limitations, MPEP section 2113 states “even though product by process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production, if the product in the product-by-process claim is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior art was made by a different process.” *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed.Cir. 1985).

With regard to the layers, collagen in combination with mineral components implicitly tends to separate into phases or layers. Note US 5,543,441, column 3 lines, 66 to column 4, line 5 is cited as art of interest to support examiner’s position.

### ***Response to Arguments***

Applicant argues that mineralized collagen matrix has a special meaning as it pertains to the field of bio-mineralization. Applicant argues that “not only does the specification provide context for the meaning of the phrase, but the specification clearly shows that the mineralized

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collagen matrix is constructed in the form of layers and at least one of the layers comprises a composite of mineralized collagen fibrils, amorphous calcium phosphate and crystalline hydroxyapatite.” Applicant argues that a mineralized collagen matrix is a intimate association between the organic and inorganic phase and it is not a simple mixture. Applicant argues that the hydroxyapatite crystals (HA) must be small enough to interact within collagen fibrils which have a size of 0.3 microns to 3000 A. Using a size that is much larger would lead to the domination of the mineral component and thereby creating a simple admixture of the collagen into the mineral matrix. Applicant provides Figures that demonstrate the difference between mineralized collagen according to the invention and a simple admixture of collagen and HA. Applicant argues that the instant mineralized collagen matrix is structurally different from a simple admixture of collagen and HA. Applicant argues that US ‘441 further supports the inventiveness of the instant invention.

Applicant's arguments filed 10/31/07 have been fully considered but they are not persuasive. The examiner notes that applicant has amended independent claim 1 to include product-by-process limitations. However, independent claims 27-28 do not have these limitations. Again the examiner points out that the specification does not define the term explicitly. Further, the specification does not state that mineralized collagen matrix excludes “simple mixtures of collagen and HA”. The examiners points to MPEP 2106 where it states, “Any special meaning assigned to a term must be sufficiently clear in the specification that any departure from common usage would be so understood by a person of experience in the field of the invention.” The applicant has not pointed to the page or pages in which the specification *explicitly* provides a definition of the term. Furthermore, the term “bone analogous coating” is



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also not defined. It is noted that the prior art of record also uses the term bone analogous.

Therefore, the examiner is permitted the broadest reasonable interpretation. Mineralize is defined by Merriam-Webster's Collegiate Dictionary as: "to impregnate or supply with mineral".

Therefore, "mineralized collagen matrix" does not preclude a "simple" mixture of collagen and HA as argued by applicant. Additionally, the examiner cites Du et al, Formation of calcium phosphate/collagen composites through mineralization of collagen matrix, Journal of Biomedical Mater Research, 2000 June 15; 50(4):518-27. Du et al teaches soaking the collagen in a calcium phosphate solution allows mineral deposition to provide mineralization of a collagen matrix. Clearly, applicant's process is not the only method of mineralizing collagen matrices. Further, it is noted that applicant argues that the intimate association is caused by nucleation of the calcium phosphate within the collagen. Constantz et al also teaches nucleation of the calcium phosphate crystals.

Regarding the product-by-process limitations, it appears applicant contends that a certain process of making the mineralized collagen matrix provides for a different structure than the prior art. The examiner directs applicant's attention to MPEP 2113. "The Patent Office bears a lesser burden of proof in making out a case of prima facie obviousness for product-by-process claims because of their peculiar nature than when a product is claimed in the conventional fashion. In re Fessmann, 489 F.2d 742, 744, 180 USPQ 324, 326 (CCPA 1974). Once the examiner provides a rationale tending to show that the claimed product appears to be the same or similar to that of the prior art, although produced by a different process, the burden shifts to applicant to come forward with **evidence** establishing an unobvious difference between the claimed product and the prior art product. In re Marosi, 710 F.2d 798, 802, 218 USPQ 289, 292

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(Fed. Cir. 1983)". However, applicant has not demonstrated with evidence how the process limitations impart a structurally defining feature compared to the prior art of record. This is critical since applicant argues that "mineralized collagen matrix" is analogous to bone and JP '259 also teaches the coating is "close to osseous tissue". Thus, applicant must show that JP's plasma spraying process makes a materially different product. It should be noted that the attorney's arguments cannot take the place of evidence. See MPEP 716.01(c) (II).

With regard to applicant's arguments that the prior art does not teach layers, the examiner cites US '441 to show that a combination of collagen and mineral is known to inherently separate into layers or phases. Also, Constantz teaches applying the HA coating in layers.

Applicant argues JP '259 is silent to a mineralized collagen fibrils, amorphous phosphate, and crystalline hydroxyapatite. Applicant argues that Constantz only teaches a similar mixture of HA, with small amount of amorphous phosphate, and collagen.

The arguments pertaining to "mineralized collagen matrix" have been discussed above. Moreover, the examiner notes that applicant has not specified the concentration of the amorphous phosphate and therefore, even "a small amount of amorphous phosphate" is enough to meet the claimed limitation.

Applicant argues that the particle size taught by Constantz is so broad it is rendered meaningless. Applicant argues that although Lussi teaches a crystal size of 100-300 nm and 100-400nm, Lussi does not teach all the particles sizes are beneficial. Applicant cites column 1, lines 42-59 and column 3, lines 58-64.

Firstly, the examiner notes that Constantz teaches a broad range; however it is applicant's burden to show the unobviousness of the instant narrow range, which is encompassed by the

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prior art. Note MPEP 2131.03. Moreover, if it is applicant's position that the instant particle size is unexpected since it provides a bone analogous coating, the examiner points out that Lussi teaches this and thus it is not unexpected.

Applicant argues that Lussi does not teach which form of natural bone is used.

The examiner points out that Lussi teaches hydroxyapatite crystals. Note example 4.

Applicant argues that Lussi is not analogous art.

The examiner directs applicant's attention to column 4, lines 25-40 wherein Lussi discloses,

The bone mineral according to the invention may thus be used as a remodelling implant **or prosthetic bone replacement**, for example in orthopedic surgery, including hip revisions, replacement of bone loss e.g. in traumatology, remodelling in maxillo facial surgery or filling periodontal defects and tooth extraction sockets.

Further JP '259 is directed to a prosthetic implant. Thus, both references are in the same field of endeavor.

Therefore, it is the examiner's position that the instant invention are rendered obvious.

**Claims 5-6 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 11-047259 in view of Constantz et al (5,279,831) optionally in view of Lussi et al (5,167,961) as evidenced by US Patent 5,543,441 in further view Sauk et al (4,780,450).**

The teachings of JP, Constantz, and Lussi, have been set forth above.

The references do not specify the instant collagen combination, i.e. type I and type III.

Sauk et al teach a composition containing particulate calcium phosphate (hydroxyapatite) and type I collagen (col. 4, lines 59-66). Sauk teaches the collagen provides a structural matrix preventing migration of the calcium particles and the calcium phosphate particles also interact with the collagen to improve the physical properties of the collagen matrix by reducing its

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compressibility and increasing its mechanical strength. Sauk teaches not only does the combination provide a scaffold for new bone ingrowth but it mimics natural bone. A mixture of type I and type III collagen is taught (example 1). Sauk et al teach in column 2, line 60 to column 3, line 5, "the composition preferably comprise a mixture of phosphophoryn calcium, a matrix material (type I collagen), and calcium phosphate ceramic.

It would have been obvious for one of ordinary skill in the art at the time the invention was made to combine the teaching of above references and Sauk et al and utilize a mixture of type I and type II collagen for the collagen matrix. One would have been motivated to do so since, as indicated by Sauk et al, this is a routine practice done at the time the invention was made.

### ***Response to Arguments***

Applicant argues that Sauk does not cure the deficiencies of JP '259, Constantz, and Lussi.

Applicant's arguments filed 5/18/07 have been fully considered but they are not persuasive. The merits of JP '259, Constantz, and Lussi have been discussed above. Since applicant has not provided any substantives arguments pertaining to this instant rejection, the rejection is maintained for the reasons of record.

**Claims 7 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 11-047259 in view of Constantz et al (5,279,831) optionally in view of Lussi et al (5,167,961) as evidenced by US Patent 5,543,441 in further view of Geistlich et al (5,573,771).**

The teachings of JP, Constantz, and Lussi, have been set forth above.

The references do not teach the use of gelatin.

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Geistlich teaches a bone mineral product that comprises collagen (Type I or Type I-III), gelatin, and calcium phosphate components. The reference teaches gelatin provides strength and freedom from antigenicity. See column 2, lines 20-30. Further, the reference teaches the use of active agents such as growth factors, antibiotics, etc to allow the bone to be used as a drug carrier. See column 3, lines 20-65.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references and further add gelatin to JP's coating composition. One would have been motivated to do so since Geistlich teaches gelatin not only adds strength to bone mineral products but it also reduces an adverse immune response.

### ***Response to Arguments***

Applicant argues that Geistlich does not cure the deficiencies of JP '259, Constantz, and Lussi. Applicant argues that Geistlich is non-analogous art.

Applicant's arguments filed 5/18/07 have been fully considered but they are not persuasive. The merits of JP '259, Constantz, and Lussi have been discussed above. The examiner directs applicant's attention to the abstract, which clearly discloses,

Such products are intended as remodeling implants or prosthetic bone replacement.

Further JP '259 is directed to a prosthetic implant. Thus, both references are in the same field of endeavor.

Therefore, it is the examiner's position that the instant invention are rendered obvious.

**Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over JP 11-047259 in view of Constantz et al (5,279,831) optionally in view of Lussi et al (5,167,961) as evidenced by US Patent 5,543,441 in further view of Liu (6,300,315).**

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The teachings of JP, Constantz, and Lussi, have been set forth above.

The references do not teach the use of additional calcium phosphates as claimed in claim 3.

Liu teaches a mineralized collagen membrane for medical applications such as bone substitutes. The mineralized collagen membrane comprises a substantially homogeneous mineralized collagen composite of about 30% to about 70% by weight of collagen component and about 30% to about 70% by weight of calcium phosphate minerals. The calcium phosphate minerals component is selected from tri-calcium phosphate, octa-calcium phosphate, amorphous calcium phosphate, hydroxyapatite, and mixture thereof. See column 3, lines 1-10 and column 5, lines 59-65. . The mineralized collagen provides mechanical properties superior compared to collagen alone. See column 3, lines 65-67. Liu teaches the membrane may also include antibiotics, bone growth factors, etc. See column 7, lines 45-50. Liu teaches the mineralized collagen membrane may include one or more additional components such as metals, such as alkali metals, other alkaline earth metals and the like. Liu teaches at lest a portion of the phosphate and/or hydroxyl content of the calcium- and phosphate-containing minerals may be replaced by a halogen, such as chloride or fluoride, carbonate and the like. See column 6, lines 1-20.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the above references and Liu and further add the instantly claimed calcium phosphates. One would have been motivated to do so since Liu teaches a mineralized collagen composition for medical applications wherein the calcium phosphate may be a mixture of different types of calcium phosphates including tricalcium phosphate, hydroxyapatite,

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amorphous calcium phosphate, octacalcium phosphate to provide a strong and flexible membrane. Further, JP teaches the coating has a small weight percent of tricalcium phosphate; thus if a skilled artisan desired to utilize octacalcium phosphate in place of tricalcium phosphate, a skilled artisan would have been motivated to substitute accordingly in view of Liu's teaching that the mineral phase may be made of a mixture of calcium phosphates.

### ***Response to Arguments***

Applicant argues that Lui does not cure the deficiencies of JP '259, Constantz, and Lussi. Applicant argues that Lui does not teach the instant HA size. Applicant also argues that Lui teaches a process of precipitating calcium phosphate, which forms a loose network

Applicant's arguments filed 5/18/07 have been fully considered but they are not persuasive. The merits of JP '259, Constantz, and Lussi have been discussed above. The examiner points out that Lui is not relied upon to teach HA particle size since Constantz and Lussi cure this deficiency. The premise of the rejection is the obviousness of utilizing a mixture of different calcium phosphates, which applicant has not addressed. Applicant's arguments pertaining to Lui's process of making the coating is irrelevant since the instant claims are not directed to a process of making a mineralized collagen matrix.

Therefore, it is the examiner's position that the instant invention are rendered obvious.

**Claims 1, 3-5, 8, 10, 12-16, 18-19, 21, 23-25, and 27-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Worch et al (6,524,718) in view of Liu (6,300,315) in further view of Lussi et al (5,167,961) as evidenced by US Patent 5,543,441.**

Worch et al disclose a metallic substrate (titanium) having a polyphase oxide coating. The polyphase oxide coating is produced by bringing the metallic substrate into contact with an

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organic and/or inorganic component to be integrated into the polyphase oxide coating such that the inorganic and/or organic phases are present at or in the direct vicinity of the substrate surface and by simultaneously or subsequently anodically polarizing the substrate material in an electrolytic solution. See abstract. The process of coating the implant yields a two-layer oxide coating, where the outer layer is the inorganic and/or the organic phase. See column 2, lines 32-45. The inorganic component is calcium phosphate and the organic component is Type I collagen. See column 2, lines 46-60. Claim 1 envisages a combination of an organic phase and inorganic phase and claim 4 envisages calcium phosphate as the inorganic phase. Example 1 discloses a coating thickness of 250 nm (.250 micrometers) on the metallic implant. Worch discloses a process wherein the metallic implant is immersed in a collagen solution at the instant pH and temperature and then coated again with a phosphate solution. Note that the use of calcium ions in this solution is clearly envisaged as noted in column 2, lines 46-60 and claim 4.

Although Worch teaches the use of calcium phosphates as the inorganic phase, Worch does not teach specify the form of calcium phosphate or the size of the calcium phosphate. Also Worch does not teach the incorporation of components as recited in claim 4 (doping agents) or 8 (medicaments).

Liu teaches a mineralized collagen membrane for medical applications such as bone substitutes. The mineralized collagen membrane comprises a substantially homogeneous mineralized collagen composite of about 30% to about 70% by weight of collagen component and about 30% to about 70% by weight of calcium phosphate minerals. The calcium phosphate minerals component is selected from tri-calcium phosphate, octa-calcium phosphate, amorphous calcium phosphate, hydroxyapatite, and mixture thereof. See column 3, lines 1-10 and column 5,



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lines 59-65. . The mineralized collagen provides mechanical properties superior compared to collagen alone. See column 3, lines 65-67. Liu teaches the membrane may also include antibiotics, bone growth factors, etc. See column 7, lines 45-50. Liu teaches the mineralized collagen membrane may include one or more additional components such as metals, such as alkali metals, other alkaline earth metals and the like. Liu teaches at least a portion of the phosphate and/or hydroxyl content of the calcium- and phosphate-containing minerals may be replaced by a halogen, such as chloride or fluoride, carbonate and the like. See column 6, lines 1-20.

Lussi et al teach a process for preparing high purity bone mineral for implantation. See abstract. Lussi teaches natural bone mineral comprises hydroxyapatitelike crystallites with a particular degree of crystallinity, habit and size (irregular platelike morphology, 5-10nm in thickness 10-50 nm in length) and surface chemistry resulting from the calcium to phosphate ratio (37.5-38.0% calcium and 15.5-5-19.0% phosphorus). See column 1, lines 15-35. Lussi teaches prior art methods of making the bone mineral result in significant increase in crystal size which is much less readily remodelled on implantation since osteoclasts and osteoblasts cannot readily perform on such large crystals the dual function of mineral resorption and generation of new bone. Such implanted inserts may thus remain unchanged indefinitely eventually giving rise to undesirable effects. Lussi teaches, alternatively, many synthetic tricalcium phosphate products tend to be resorbed too rapidly for osteoblasts to regenerate new bone. See column 1, lines 49-60. The process provides HA particles having a size from 20nm to 250; 100nm to 300nm; and 100nm to 400nm and a diameter of 34nm or 130 nm depending on the temperature used. See Table 1. Lussi teaches the HA particles have a similar structure to original bone. See column 4,

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lines 1-10. Lussi teaches it is important to avoid modification of the crystal sizes to ensure when the bone is implanted, it is readily converted into natural bone. See column 5, lines 18-30. The bone mineral according to the invention may thus be used as a remodelling implant or prosthetic bone replacement, for example in orthopedic surgery, including hip revisions, replacement of bone loss e.g. in traumatology, remodelling in maxillo facial surgery or filling periodontal defects and tooth extraction sockets. The bone mineral may also have adsorbed or absorbed therein one or more physiologically active substances including drugs or polypeptides, and proteins. See column 4, lines 30-60 and column 5, lines 10-20. .

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Worch and Liu and utilize the instantly claimed calcium phosphates. One would have been motivated to do so since Liu teaches a mineralized collagen composition for medical applications wherein the calcium phosphate may be a mixture of different types of calcium phosphates including hydroxyapatite and amorphous calcium phosphate to provide a strong and flexible membrane. Thus, it would have been obvious to utilize the instantly claimed calcium phosphates since Liu demonstrates the state of the art wherein it is known to add the instantly claimed calcium phosphates with collagen. Further, Worch teaches the combination of calcium phosphate phases and collagen wherein it is clear that Worch contemplates utilizing more than one form of calcium phosphate. Further, on column 1, lines 45-55, Worch states the deficiency of the prior art is that it only utilizes resorbable calcium phosphate and not hydroxyapatite and thus “the complete character of the implant is lost”. Thus, one would have expected success with the instant combination since Worch implicitly teaches a combination of hydroxyapatite and resorbable calcium phosphate (not crystallized calcium

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phosphate). With regard to the instantly claimed doping agents, it would have been obvious to dope Worch's mineralized collagen since Liu teaches the adding minor portions of fluoride or carbonate to the mineralized collagen to provide certain desired properties and to resemble or simulate biological apatite. With regard to the instantly claimed drugs, it would have been obvious to add certain drugs depending on the desired effect of the implant as taught by Liu.

Secondly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teaching of Worch, Liu, and Lussi et al and utilize the instant particle size. One would have been motivated to do so since Lussi teaches that HA particles with the instant particle size resorb better and cause generation of new bone faster. Further, Lussi teaches natural bone has the instant particle size. Thus, a skilled artisan would have been motivated to utilize the instant particle size since it closely resembles natural bone and allows for the body to convert the particles to natural bone faster.

Regarding the product-by-process limitations, MPEP section 2113 states "even though product by process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production, if the product in the product-by-process claim is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior art was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed.Cir. 1985).

With regard to the layers, it is the examiner's position that collagen in combination with mineral components implicitly tends to separate into phases or layers. US Patent 5,543,441 column 3 lines, 66 to column 4, line 5 is cited as art of interest to support examiner's position.

***Response to Arguments***

Applicant argues that the inorganic phase does not form multiple layers. Applicant argues that the claims have been amended to recite the coating is “adhered to the metallic implant which overcomes the rejection over Worch et al. Applicant argues that the coating of Worch are embedded in the oxide surface of the implant and not deposited on the implant surface. Applicant argues that Worch describes an electrochemical coating process which uses a anodic polarization process.

Applicant's arguments filed 10/31/07 have been fully considered but they are not persuasive. Applicant has not defined adhered and therefore the examiner is entitled to utilize the broadest *reasonable* interpretation. Secondly, the definition of adhered is to: To stick fast by or as if by suction or glue. To cause to adhere; make stick. Merriam Webster defines adhere as “to hold fast or stick by or as if by gluing suctions, grasping, or fusing.” The examiner points out that term “adhered to” does not exclude embedding since embedding is a way of joining (sticking or fusing) two surfaces together. Worch discloses the phases are integrated by adsorption, sedimentation application, or deposition. See column 2, line 65 to column 3, line 5. Worch also discloses that the inorganic and organic phases are integrated into the oxide phase and extend beyond it. See claim 23. Additionally, Worch discloses the metallic implant is inserted into a collagen solution so that the collagen fibrillae adsorb to the surface of the implant. The examiner notes that the instant examples of the specification also immerse the implant into the collagen solution at the same pH and temperature. Applicant has not provided any persuasive arguments to overcome the rejection.

Regarding the product-by-process limitations, it appears applicant contends that a certain process of making the mineralized collagen matrix provides for a different structure than the

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prior art. The examiner directs applicant's attention to MPEP 2113. "The Patent Office bears a lesser burden of proof in making out a case of prima facie obviousness for product-by-process claims because of their peculiar nature than when a product is claimed in the conventional fashion. In re Fessmann, 489 F.2d 742, 744, 180 USPQ 324, 326 (CCPA 1974). Once the examiner provides a rationale tending to show that the claimed product appears to be the same or similar to that of the prior art, although produced by a different process, the burden shifts to applicant to come forward with **evidence** establishing an unobvious difference between the claimed product and the prior art product. In re Marosi, 710 F.2d 798, 802, 218 USPQ 289, 292 (Fed. Cir. 1983)". However, applicant has not demonstrated with evidence how the process limitations impart a structurally defining feature compared to the prior art of record. This is critical since applicant argues that the only difference in the process is that Worch uses a anodic polarization process. It should be noted that the attorney's arguments cannot take the place of evidence. See MPEP 716.01(c) (II).

Therefore, it is the examiner's position that the Worch in view of Liu in further view of Lussi renders the instant invention obvious.

**Claims 6 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Worch et al (6,524,718) in view of Liu (6,300,315) in view of Lussi et al (5,167,961) as evidenced by US Patent 5,543,441 in further view of Sauk et al (4,780,450).**

The teachings of Worch, Liu, and Lussi, have been set forth above.

The references do not specify the instant collagen combination, i.e. type I and type III.

Sauk et al disclose a composition containing particulate calcium phosphate (hydroxyapatite) and type I collagen (col. 4, lines 59-66). A mixture of type I and type III

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collagen is taught (example 1). Sauk et al disclose in column 2, line 60 to column 3, line 5, “the composition preferably comprise a mixture of phosphophoryn calcium, a matrix material (type I collagen), and calcium phosphate ceramic. These compositions are intended to facilitate matrix-mediated mineralization, whereby the collagen defines a structural matrix and the salt regulates and directs mineral deposition in terms of its location, crystallinity and association with the calcium phosphate ceramic particles.

It would have been obvious for one of ordinary skill in the art at the time the invention was made to combine the teaching of Worch, Liu, Lussi, and Sauk et al and utilize a mixture of type I and type II collagen for the collagen matrix. One would have been motivated to do so since, as indicated by Sauk et al, this is a routine practice done at the time the invention was made.

#### ***Response to Arguments***

Applicant has not argued the merits of this rejection and therefore it is the examiner’s position that the instant claims are rendered obvious for the reasons of record.

**Claims 1, 3-4, 8, 10, 12--16, 18-19, 21, 23-25, and 27-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shirkanzadeh (5,205,921) in view of Liu (6,300,315) in further view of Lussi et al (5,167,961) as evidenced by US Patent 5,543,441.**

Shirkanzadeh discloses a method of depositing bioactive coatings on conductive substrates wherein a cathode and D.C. potential is applied to raise the interfacial pH at the cathode sufficiently enough to precipitate the desired oxide or phosphate thereon as a dense adherent film. See abstract. The substrate can be titanium alloy or steel and the coating is 50 microns thick for a uniform, continuous, and firmly bonded coating. See example 4. The coating

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composition includes calcium phosphate and non-toxic biological compounds, i.e. collagen. The inorganic compounds, i.e. calcium phosphate, may be co-precipitated with the organic compounds, i.e. collagen. This process allows the doping of specific ions in calcium phosphate crystals. See column 3, lines 5-20. Preferably crystalline calcium phosphate is utilized compared to amorphous calcium phosphate. The calcium phosphate is selected from either tricalcium phosphate and hydroxyapatite is taught. See claims and examples. The micropores in the calcium phosphate compound coating also encourages better adhesion of collagen. The instant doping agents (carbonate and fluoride) are taught in the electrolyte solution.

The reference does not teach the combination of amorphous calcium phosphate and hydroxyapatite (HA) or the instant particle size of HA.

Liu teaches a mineralized collagen membrane for medical applications such as bone substitutes. The mineralized collagen membrane comprises a substantially homogeneous mineralized collagen composite of about 30% to about 70% by weight of collagen component and about 30% to about 70% by weight of calcium phosphate minerals. The calcium phosphate minerals component is selected from tri-calcium phosphate, octa-calcium phosphate, amorphous calcium phosphate, hydroxyapatite (HA), and mixture thereof. See column 3, lines 1-10 and column 5, lines 59-65. . The mineralized collagen provides mechanical properties superior compared to collagen alone. See column 3, lines 65-67. Liu teaches the membrane may also include antibiotics, bone growth factors, etc. See column 7, lines 45-50. Liu teaches the mineralized collagen membrane may include one or more additional components such as metals, such as alkali metals, other alkaline earth metals and the like. Liu teaches at least a portion of the phosphate and/or hydroxyl content of the calcium- and phosphate-containing minerals may be

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replaced by a halogen, such as chloride or fluoride, carbonate and the like. See column 6, lines 1-20.

Lussi et al teach a process for preparing high purity bone mineral for implantation. See abstract. Lussi teaches natural bone mineral comprises hydroxyapatite-like crystallites with a particular degree of crystallinity, habit and size (irregular platelike morphology, 5-10nm in thickness 10-50 nm in length) and surface chemistry resulting from the calcium to phosphate ratio (37.5-38.0% calcium and 15.5-5-19.0% phosphorus). See column 1, lines 15-35. Lussi teaches prior art methods of making the bone mineral result in significant increase in crystal size which is much less readily remodelled on implantation since osteoclasts and osteoblasts cannot readily perform on such large crystals the dual function of mineral resorption and generation of new bone. Such implanted inserts may thus remain unchanged indefinitely eventually giving rise to undesirable effects. Lussi teaches, alternatively, many synthetic tricalcium phosphate products tend to be resorbed too rapidly for osteoblasts to regenerate new bone. See column 1, lines 49-60. The process provides HA particles having a size from 20nm to 250; 100nm to 300nm; and 100nm to 400nm and a diameter of 34nm or 130 nm depending on the temperature used. See Table 1. Lussi teaches the HA particles have a similar structure to original bone. See column 4, lines 1-10. Lussi teaches it is important to avoid modification of the crystal sizes to ensure when the bone is implanted, it is readily converted into natural bone. See column 5, lines 18-30. The bone mineral according to the invention may thus be used as a remodelling implant or prosthetic bone replacement, for example in orthopedic surgery, including hip revisions, replacement of bone loss e.g. in traumatology, remodelling in maxillo facial surgery or filling periodontal defects and tooth extraction sockets. The bone mineral may also have adsorbed or absorbed



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therein one or more physiologically active substances including drugs or polypeptides, and proteins. See column 4, lines 30-60 and column 5, lines 10-20. .

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Shirkanzadeh and Liu and utilize the instantly claimed calcium phosphates. One would have been motivated to do so since Liu teaches a mineralized collagen composition for medical applications wherein the calcium phosphate may be a mixture of different types of calcium phosphates including hydroxyapatite and amorphous calcium phosphate to provide a strong and flexible membrane. Thus, it would have been obvious to utilize the instantly claimed calcium phosphates since Liu demonstrates the state of the art wherein it is known to add the instantly claimed calcium phosphates with collagen.

Secondly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teaching of Shirkanzadeh, Liu, and Lussi et al and utilize the instant particle size. One would have been motivated to do so since Lussi teaches that HA particles with the instant particle size resorb better and cause generation of new bone faster. Further, Lussi teaches natural bone has the instant particle size. It is noted that although Shirkanzadeh teaches the final coating comprises a network of crystals with a size of 2-5 microns, Shirkanzadeh does not teach away from using other particle sizes. Thus, a skilled artisan would have been motivated to utilize the instant particle size since it closely resembles natural bone and allows for the body to convert the particles to natural bone faster.

Regarding the product-by-process limitations, MPEP section 2113 states “even though product by process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its

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method of production, if the product in the product-by-process claim is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior art was made by a different process.” *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed.Cir. 1985). It is noted that

With regard to layers, it is noted that collagen in combination with mineral components implicitly tends to separate into phases or layers. US Patent 5,543,441 column 3 lines, 66 to column 4, line 5 is cited as art of interest to support examiner’s argument.

### ***Response to Arguments***

Applicant argues the particle sizes taught by Shirkanzadeh are too large to promote mineralization and thus does not resemble native bone. Applicant argues that an electrochemical precipitation process requires charged particles and Lui’s particles do not possess an charges. Applicant argues that therefore the combine would not provide the instant coating. Applicant argues that Lussi teaches away from the instant particle size.

Applicant’s arguments filed 10/31/07 have been fully considered but they are not persuasive. The examiner notes that Shirkanzadeh does not teach the instant particle sizes and thus the examiner relies on the Lussi. The merits of Lussi have been discussed above and are incorporated herein. It is noted that applicant argues that Lussi does not teach a skilled artisan to utilize a particle size of 20-400nm. The examiner points out that applicant is claiming a range of about 300-500nm and not 20-400nm. Moreover, independent claim 26 does not recite any particle range.

The examiner notes that Shirkanzadeh is not limited to charged particles and applicant has not cited any specific column or line in which Shirkanzadeh requires only charged particles.

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Moreover, applicant has not cited any specific column or line in which Lui teaches away from an electric charge. Therefore, this argument is unpersuasive since Shirkanzadeh applies a DC potential to charge particles. Therefore, the mineral used need not have a charge.

With regard to applicant's arguments that the prior art does not teach layers, the examiner cites US '441 to show that a combination of collagen and mineral is known to inherently separate into layers or phases.

Therefore, it is the examiner's position that the instant invention are rendered obvious.

**Claims 5-6 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shirkanzadeh (5,205,921) in view of Liu (6,300,315) in view of Lussi et al (5,167,961) as evidenced by US Patent 5,543,441 in view of Sauk et al (4,780,450).**

Shirkanzadeh discloses a method of depositing bioactive coatings on conductive substrates wherein a cathode and D.C. potential is applied to raise the interfacial pH at the cathode sufficiently enough to precipitate the desired oxide or phosphate thereon as a dense adherent film. See abstract. The substrate can be titanium alloy or steel and the coating is 50 microns thick for a uniform, continuous, and firmly bonded coating. See example 4. The coating composition includes calcium phosphate and non-toxic biological compounds, i.e. collagen. The inorganic compounds, i.e. calcium phosphate, may be co-precipitated with the organic compounds, i.e. collagen. This process allows the doping of specific ions in calcium phosphate crystals. See column 3, lines 5-20. Preferably crystalline calcium phosphate is utilized compared to amorphous calcium phosphate. The particle range of the calcium phosphate is 2-5 microns. See example 2. The instant doping agents (carbonate and fluoride) are taught in the electrolyte solution.

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The reference does not specify the instant collagen combination, i.e. type I and type III.

Sauk et al disclose a composition containing particulate calcium phosphate (hydroxyapatite) and type I collagen (col. 4, lines 59-66). A mixture of type I and type III collagen is taught (example 1). Sauk et al disclose in column 2, line 60 to column 3, line 5, “the composition preferably comprise a mixture of phosphophoryn calcium, a matrix material (type I collagen), and calcium phosphate ceramic. These compositions are intended to facilitate matrix-mediated mineralization, whereby the collagen defines a structural matrix and the salt regulates and directs mineral deposition in terms of its location, crystallinity and association with the calcium phosphate ceramic particles.

It would have been obvious for one of ordinary skill in the art at the time the invention was made to combine the teaching of Shirkanzadeh et al and Sauk et al and utilize a mixture of type I and type II collagen for the collagen matrix. One would have been motivated to do so since, as indicated by Sauk et al, this is a routine practice done at the time the invention was made.

#### ***Response to Arguments***

Applicant has not argued the merits of this rejection and therefore it is the examiner's position that the instant claims are rendered obvious for the reasons of record.

**Claims 7 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shirkanzadeh (5,205,921) in view of Liu (6,300,315) in view of Lussi et al (5,167,961) as evidenced by US Patent 5,543,441 in further view of Geistlich et al (5,573,771).**

The teachings of Shirkanzadeh, Lui, and Lussi, have been set forth above.

The references do not teach the use of gelatin.

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Geistlich teaches a bone mineral product that comprises collagen (Type I or Type I-III), gelatin, and calcium phosphate components. The reference teaches gelatin provides strength and freedom from antigenicity. See column 2, lines 20-30. Further, the reference teaches the use of active agents such as growth factors, antibiotics, etc to allow the bone to be used as a drug carrier. See column 3, lines 20-65.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references and further add gelatin to the coating composition. One would have been motivated to do so since Geistlich teaches gelatin not only adds strength to bone mineral products but it also reduces an adverse immune response.

**Claims 1, 3-6, 8, 10, 12-16, 18-19, 23-25, 27-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Constantz et al (5,279,831) in view of Liu (6,300,315) optionally in further view of Lussi et al (5,167,961) and as evidenced by US 5,543,441.**

Constantz teaches a hydroxyapatite prosthesis coating which allows for ingrowth of natural bone. See abstract. The method involves combining a soluble source of calcium with a soluble source of phosphate under conditions of controlled nucleation and modulated crystal growth to form a multilayered hydroxyapatite coating on a substrate. Constantz teaches the use of other ions and components to modify the HA composition such as using fluoride, carbonate, hydrogen, etc, which influence the dissolution behavior of the coating. see column 2, lines 50-60. Constantz teaches the coating composition may further comprises collagen and growth factors to enhance bony ingrowth. See column 6, lines 1-10. The composition is coated on a steel or titanium. See column 6, lines 14-20. The crystals have a diameter of 0.01microns (10nm) to 20 microns (20000nm) (see column 2, line 60) and a length of 0.01 microns (10nm) to about 10

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microns (10000nm) (see column 3, line 40). Constantz teaches a first layer of the coating with a thickness of 0.01microns (10nm) to 20 microns (20000nm). See column 3, lines 39-41.

Constantz does not teach the use of amorphous calcium phosphate or additional calcium phosphates as claimed in claim 3.

Liu teaches a mineralized collagen membrane for medical applications such as bone substitutes. Liu teaches the mineralized collagen membrane is thin, strong, and flexible. The mineralized collagen membrane comprises a substantially homogeneous mineralized collagen composite of about 30% to about 70% by weight of collagen component and about 30% to about 70% by weight of calcium phosphate minerals. The calcium phosphate mineral component is selected from tri-calcium phosphate, octa-calcium phosphate, amorphous calcium phosphate, hydroxyapatite, and mixture thereof. See column 3, lines 1-10 and column 5, lines 59-65. The mineralized collagen provides mechanical properties superior compared to collagen alone. See column 3, lines 65-67. Liu teaches the membrane may also include antibiotics, bone growth factors, etc. See column 7, lines 45-50. Liu teaches the mineralized collagen membrane may include one or more additional components such as metals, such as alkali metals, other alkaline earth metals and the like. Liu teaches at least a portion of the phosphate and/or hydroxyl content of the calcium- and phosphate-containing minerals may be replaced by a halogen, such as chloride or fluoride, carbonate and the like. See column 6, lines 1-20.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Worch and Liu and utilize the instantly claimed calcium phosphates. One would have been motivated to do so since Liu teaches a mineralized collagen composition for medical applications wherein the calcium phosphate may be a mixture of

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different types of calcium phosphates including hydroxyapatite and amorphous calcium phosphate to provide a strong and flexible membrane. Thus, it would have been obvious to utilize the instantly claimed calcium phosphates since Liu demonstrates the state of the art wherein it is known to add the instantly claimed calcium phosphates with collagen.

Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teaching of JP and Lussi et al and specifically utilize the instant particle size. One would have been motivated to do so since Lussi teaches that HA particles with the instant particle size resorb better and cause generation of new bone faster. Further, Lussi teaches natural bone has the instant particle size. Thus, a skilled artisan would have been motivated to utilize the instant particle size since it closely resembles natural bone and allows for the body to convert the particles to natural bone faster. A skilled artisan would have reasonably expected similar results since JP teaches the purpose of the hydroxyapatite coating on implants since to provide a surface for bone ingrowth and to mimic natural bone.

Regarding the product-by-process limitations, MPEP section 2113 states “even though product by process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production, if the product in the product-by-process claim is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior art was made by a different process.” *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed.Cir. 1985).

With regard to the layers, collagen in combination with mineral components implicitly tends to separate into phases or layers. Note US 5,543,441, column 3 lines, 66 to column 4, line 5 is cited as art of interest to support examiner’s position.

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**Claims 5-6 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Constantz et al (5,279,831) in view of Liu (6,300,315) optionally in view of Lussi et al (5,167,961) as evidenced by US Patent 5,543,441 in further view Sauk et al (4,780,450).**

The teachings of Constantz, Liu, and Lussi, have been set forth above.

The references do not specify the instant collagen combination, i.e. type I and type III.

Sauk et al teach a composition containing particulate calcium phosphate (hydroxyapatite) and type I collagen (col. 4, lines 59-66). Sauk teaches the collagen provides a structural matrix preventing migration of the calcium particles and the calcium phosphate particles also interact with the collagen to improve the physical properties of the collagen matrix by reducing its compressibility and increasing its mechanical strength. Sauk teaches not only does the combination provide a scaffold for new bone ingrowth but it mimics natural bone. A mixture of type I and type III collagen is taught (example 1). Sauk et al teach in column 2, line 60 to column 3, line 5, "the composition preferably comprise a mixture of phosphophoryn calcium, a matrix material (type I collagen), and calcium phosphate ceramic.

It would have been obvious for one of ordinary skill in the art at the time the invention was made to combine the teaching of above references and Sauk et al and utilize a mixture of type I and type II collagen for the collagen matrix. One would have been motivated to do so since, as indicated by Sauk et al, this is a routine practice done in the implant art at the time the invention was made.

### ***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection



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is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

**Claims 1, 3-5, 8, 10-16, 18-19, 21, 23-25, and 27-28 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-23 of U.S. Patent No. 6,524,718 in view of in view of Liu (6,300,315) in view of Lussi et al (5,167,961).**

Claim 1 is directed to a coated metallic implant comprising a metallic implant and an outer layer, wherein the outer layer comprises a bone analogous coating comprising a collagen matrix mineralized with a calcium phosphate phase which is adhered to said implant surface, wherein the mineralized collagen matrix is constructed in the form of layers and each layer comprises a network of mineralized collagen fibrils, amorphous calcium phosphate clusters, and crystalline hydroxyapatite.

US patent is directed to a metallic object and a thin polyphase oxide coating, where said polyphase oxide coating is comprised of a first phase, wherein said first phase is a metal oxide phase, and a second phase, wherein said second phase is either an organic phase, an inorganic phase, or a combination of organic and inorganic phases, said polyphase oxide coating is

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produced by bringing the metallic substrate into contact with either an organic component, an inorganic component, or a combination of organic and inorganic components to be integrated into said polyphase oxide coating such that said second phase is present at or adjacent to the substrate surface and by simultaneously or subsequently anodically polarizing said substrate material in an electrolytic solution, wherein said metallic substrate is selected from the group consisting of aluminum, titanium, tantalum, zirconium, niobium, or their alloys, inclusive of intermetallic phases. Dependent claims are directed to the organic phases comprising collagen and the inorganic phases comprising calcium phosphate phases.

Liu teaches a mineralized collagen membrane for medical applications such as bone substitutes. The mineralized collagen membrane comprises a substantially homogeneous mineralized collagen composite of about 30% to about 70% by weight of collagen component and about 30% to about 70% by weight of calcium phosphate minerals. The calcium phosphate minerals component is selected from tri-calcium phosphate, octa-calcium phosphate, amorphous calcium phosphate, hydroxyapatite, and mixture thereof. See column 3, lines 1-10 and column 5, lines 59-65. : The mineralized collagen provides mechanical properties superior compared to collagen alone. See column 3, lines 65-67. Liu teaches the membrane may also include antibiotics, bone growth factors, etc. See column 7, lines 45-50. Liu teaches the mineralized collagen membrane may include one or more additional components such as metals, such as alkali metals, other alkaline earth metals and the like. Liu teaches at least a portion of the phosphate and/or hydroxyl content of the calcium- and phosphate-containing minerals may be replaced by a halogen, such as chloride or fluoride, carbonate and the like. See column 6, lines 1-20.

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Lussi et al teach a process for preparing high purity bone mineral for implantation. See abstract. Lussi teaches natural bone mineral comprises hydroxyapatitelike crystallites with a particular degree of crystallinity, habit and size (irregular platelike morphology, 5-10nm in thickness 10-50 nm in length) and surface chemistry resulting from the calcium to phosphate ratio (37.5-38.0% calcium and 15.5-5-19.0% phosphorus). See column 1, lines 15-35. Lussi teaches prior art methods of making the bone mineral result in significant increase in crystal size which is much less readily remodelled on implantation since osteoclasts and osteoblasts cannot readily perform on such large crystals the dual function of mineral resorption and generation of new bone. Such implanted inserts may thus remain unchanged indefinitely eventually giving rise to undesirable effects. Lussi teaches, alternatively, many synthetic tricalcium phosphate products tend to be resorbed too rapidly for osteoblasts to regenerate new bone. See column 1, lines 49-60. The process provides HA particles having a size from 20nm to 250; 100nm to 300nm; and 100nm to 400nm and a diameter of 34nm or 130 nm depending on the temperature used. See Table 1. Lussi teaches the HA particles have a similar structure to original bone. See column 4, lines 1-10. Lussi teaches it is important to avoid modification of the crystal sizes to ensure when the bone is implanted, it is readily converted into natural bone. See column 5, lines 18-30. The bone mineral according to the invention may thus be used as a remodelling implant or prosthetic bone replacement, for example in orthopedic surgery, including hip revisions, replacement of bone loss e.g. in traumatology, remodelling in maxillo facial surgery or filling periodontal defects and tooth extraction sockets. The bone mineral may also have adsorbed or absorbed therein one or more physiologically active substances including drugs or polypeptides, and proteins. See column 4, lines 30-60 and column 5, lines 10-20.

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The difference between instant claims and US patent's claims is that the independent claim 1 requires specific calcium phosphates, i.e. hydroxyapatite and amorphous calcium phosphate. However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the instantly claimed calcium phosphates and arrive at the instantly claimed invention. One would have been motivated to do so since Liu teaches a mineralized collagen composition for medical applications wherein the calcium phosphate may be a mixture of different types of calcium phosphates including hydroxyapatite and amorphous calcium phosphate to provide a strong and flexible membrane. Thus, it would have been obvious to utilize the instantly claimed calcium phosphates since Liu demonstrates the state of the art wherein it is known to add the instantly claimed calcium phosphates with collagen. Further, Worch teaches the combination of calcium phosphate phases and collagen wherein it is clear that Worch envisages utilizing more than one form of calcium phosphate in claim 4. Thus, the instantly claimed calcium phosphate types are considered an obvious modification. Note that the instant claims have comprising language and thus do not exclude the oxide coating. Note the instant claims are rejected over the process claims of US patent since one would necessarily have the coated metallic implant of the instant invention by the process of making and a restriction was not made in US '718. With regard to the instantly claimed doping agents, it would have been obvious to dope Worch's mineralized collagen since Liu teaches the adding minor portions of fluoride or carbonate to the mineralized collagen to provide certain desired properties and to resemble or simulate biological apatite.

With regard to the instantly claimed drugs, it would have been obvious to add certain drugs depending on the desired effect of the implant as taught by Liu.

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Further, the instant claims differ from US patent claims in that they recite a specific HA size. It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teaching of Rhee et al and Lussi et al and utilize the instant particle size. One would have been motivated to do so since Lussi teaches that HA particles with the instant particle size resorb better and cause generation of new bone faster. Further, Lussi teaches natural bone has the instant particle size. Thus, a skilled artisan would have been motivated to utilize the instant particle size since it closely resembles natural bone and allows for the body to convert the particles to natural bone faster.

#### ***Response to Arguments***

Applicant has not argued the merits of this rejection and therefore it is the examiner's position that the instant claims are rendered obvious for the reasons of record.

#### ***Conclusion***

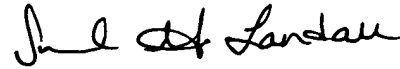
All the claims are rejected at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharmila Gollamudi Landau whose telephone number is 571-272-0614. The examiner can normally be reached on M-F (8:00-5:30), alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on 571-272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Sharmila Gollamudi Landau  
Primary Examiner  
Art Unit 1611

SGL

1/29/08